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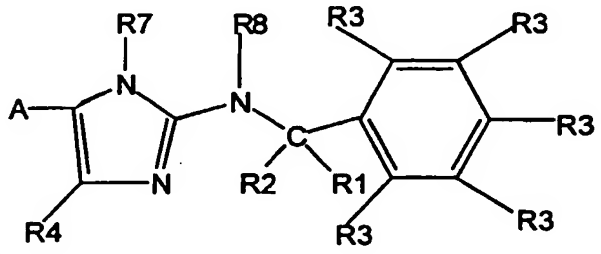
(54) Title: N-(1-PHENYLETHYL)-5-PHENYL-IMIDAZOLE-2-AMINE COMPOUNDS, THEIR COMPOSITIONS AND USES



(I)

(57) Abstract: The subject invention involves compounds having structure (I): wherein each R1 is independently alkyl, aryl, or heterocycle; each R2, R4, R7, and R8 is independently hydrogen or other substituent; A is aryl or heterocycle; and pharmaceutically acceptable forms thereof. The subject invention also involves pharmaceutical compositions containing such compounds, and methods for treating or preventing diseases or disorders using such compounds.

N-(1-PHENYLETHYL)-5-PHENYL-IMIDAZOLE-2-AMINE COMPOUNDS, THEIR COMPOSITIONS AND USES

CROSS-REFERENCE TO RELATED APPLICATIONS

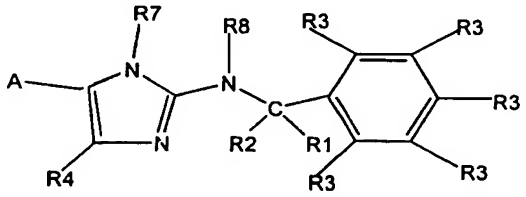
This application claims the benefit of US Provisional Application No. 60/172,709 filed December 17, 1999 and US Provisional Application No. 60/192,811, filed March 29, 2000.

FIELD OF THE INVENTION

The subject invention relates to novel imidazo-containing compounds, pharmaceutical compositions containing them, and their therapeutic or preventative use in the areas of cardiovascular, oncology, infectious and inflammatory diseases.

SUMMARY OF THE INVENTION

The subject invention includes compounds having the structure:



wherein:

(a) R1 is selected from alkyl, aryl, and heterocycle;

(b) R2 is selected from hydrogen, alkyl, aryl, and heterocycle;

(c) each R3 is independently selected from hydrogen, halo, alkyl, aryl, heterocycle, nitro, cyano, and unsubstituted or alkyl- or aryl- or heterocycle-substituted hydroxy, thio, amino, amide, formyl (acyl), carboxy, and carboxamide; two R3's on adjacent carbons may optionally together be

alkylene or heteroalkylene, thereby forming a fused ring with the phenyl to which they are attached;

(d) R4 is selected from hydrogen, halo, alkyl, aryl, heterocycle, and carboxy and its alkyl and aryl esters and amides;

(e) R7 is selected from hydrogen, alkyl, aryl, and heterocycle;

(f) R8 is selected from hydrogen, alkyl, alkylacyl, arylacyl, alkylsulfonyl, and arylsulfonyl;

(g) A is aryl or heterocycle;

and an optical isomer, diestereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof.

The subject invention also includes compositions comprising a subject compound and a pharmaceutically-acceptable excipient; and methods for treating or preventing diseases or disorders by administering to a human or lower animal in need thereof, a safe and effective amount of a subject compound.

DETAILED DESCRIPTION OF THE INVENTION

As used herein unless specified otherwise, "alkyl" means a hydrocarbon chain which is branched, linear or cyclic, saturated or unsaturated (but not aromatic), substituted or unsubstituted. The term "alkyl" may be used alone or as part of another word where it may be shortened to "alk" (e.g., in alkoxy, alkylacyl). Preferred linear alkyl have from one to about twenty carbon atoms, more preferably from one to about ten carbon atoms, more preferably still from one to about six carbon atoms, still more preferably from one to about four carbon atoms; most preferred are methyl or ethyl. Preferred cyclic and branched alkyl have from three to about twenty carbon atoms, more preferably from three to about ten carbon atoms, more preferably still from three to about seven carbon atoms, still more preferably from three to about five carbon atoms. Preferred cyclic alkyl have one hydrocarbon ring, but may have two, three, or more, fused hydrocarbon rings. Preferred alkyl are unsaturated with from one to about three double or triple bonds, preferably double bonds; more preferably they are mono-unsaturated with one double bond. Still more preferred alkyl are saturated. Saturated alkyl are referred to herein as "alkanyl". Alkyl unsaturated only with one or more double

bonds (no triple bonds) are referred to herein as "alkenyl". Preferred substituents of alkyl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, nitro, and cyano. Also, unsubstituted alkyl are preferred.

As used herein, "heteroatom" means a nitrogen, oxygen, or sulfur atom.

As used herein, "alkylene" means an alkyl which connects two other moieties, "heteroalkylene" means an alkylene having one or more heteroatoms in the connecting chain.

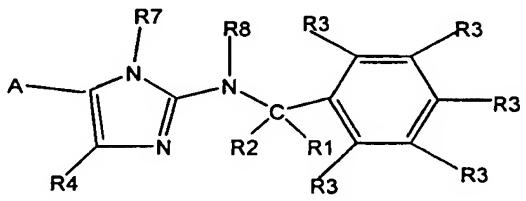
As used herein unless specified otherwise, "aryl" means an aromatic hydrocarbon ring (or fused rings) which is substituted or unsubstituted. The term "aryl" may be used alone or as part of another word (e.g., in aryloxy, arylacyl). Preferred aryl have from six to about fourteen, preferably to about ten, carbon atoms in the aromatic ring(s), and a total of from about six to about twenty, preferably to about twelve, carbon atoms. Preferred aryl is phenyl or naphthyl; most preferred is phenyl. Preferred substituents of aryl include halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides, nitro, and cyano. Also, unsubstituted aryl are preferred.

As used herein unless specified otherwise, "heterocycle" means a saturated, unsaturated or aromatic cyclic hydrocarbon ring (or fused rings) with one or more heteroatoms in the hydrocarbon ring(s). Preferred heterocycles have from one to about six heteroatoms in the ring(s), more preferably one or two or three heteroatoms in the ring(s). Preferred heterocycles have from three to about fourteen, preferably to about ten, carbon plus heteroatoms in the ring(s), more preferably from three to about seven, more preferably still five or six, carbon plus heteroatoms in the rings(s); and a total of from three to about twenty carbon plus heteroatoms, more preferably from three to about ten, more preferably still five or six, carbon plus heteroatoms. Preferred heterocycles have one ring, but may have two, three, or more, fused rings. More preferred heterocycle rings include those which are one ring with 5 or 6 carbon plus heteroatoms in the ring

with no more than three ring heteroatoms, no more than two of which are O and S. Still more preferred are such 5- or 6-ring atom heterocycles with one or two ring atoms being O or S and the others being C; or with one, two or three ring atoms being N and the others being C. Such preferred 5- or 6-ring atom heterocycles are preferably saturated, unsaturated with one or two double bonds, or aromatic. Such preferred 5- or 6-ring atom heterocycles are preferably a single ring; or fused with a 3- to 6-ring atom hydrocarbon ring which is saturated, unsaturated with one double bond, or aromatic (phenyl); or fused with another such 5- or 6-ring atom heterocyclic ring. Heterocycles are unsubstituted or substituted. Preferred heterocycle substituents are the same as for alkyl.

Compounds of the Invention

The subject invention involves compounds having the following structure:



1

In structure 1, R1 is selected from alkyl, aryl, and heterocycle. Preferred R1 includes linear alkanyl having from 1 to about 6 carbon atoms, linear alkenyl having from 2 to about 6 carbon atoms, and branched and cyclic alkanyl and alkenyl having from 3 to about 6 carbon atoms, such alkenyl preferably having 1 double bond. Such preferred alkanyl and alkenyl are preferably unsubstituted or substituted; if substituted, preferably with aryl, heterocycle, amino, hydroxy, cyano, carboxy and its esters and amides; more preferably with phenyl, heterocycle having 5 or 6 ring atoms, carboxy and its C_1-C_6 alkyl and phenyl esters, or cyano. More preferably such alkanyl and alkenyl have up to about 5 carbon atoms, more preferably still up to 4 carbon atoms. More preferred R1 is methyl, ethyl or isopropyl. Most preferred R1 is unsubstituted methyl.

In structure 1, R2 is selected from hydrogen, alkyl, aryl, and heterocycle. Preferred R2 includes hydrogen, linear alkanyl having from 1 to about 6 carbon atoms, linear alkenyl

having from 2 to about 6 carbon atoms, and branched and cyclic alkanyl and alkenyl having from 3 to about 6 carbon atoms, such alkenyl preferably having 1 double bond. Such preferred alkanyl and alkenyl are preferably unsubstituted or substituted; if substituted, preferably with aryl, heterocycle, amino, hydroxy, cyano, carboxy and its esters and amides; more preferably with phenyl, heterocycle having 5 or 6 ring atoms, carboxy and its C_1-C_6 alkyl and phenyl esters, or cyano. More preferably such alkanyl and alkenyl have up to about 5 carbon atoms, more preferably still up to 4 carbon atoms. More preferred R1 is methyl, ethyl or isopropyl. Most preferred R1 is hydrogen.

In structure 1, each R3 is each independently selected from hydrogen, halo, alkyl, aryl, heterocycle, nitro and cyano; also from hydroxy, thio, amino, amide, formyl (acyl), carboxy, and carboxamide which are unsubstituted or substituted, preferably with alkyl or aryl or heterocycle; or two R3 together are alkylene or heteroalkylene attached to adjacent carbon atoms of the phenyl ring, thereby forming a cycloalkyl or aryl or heterocycle ring which is fused to the phenyl ring. Preferred R3 are independently selected from hydrogen, halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl or aryl esters and amides; more preferably from hydrogen, halo, C_1-C_4 alkyl, thio, C_1-C_4 alkylthio, C_1-C_4 mono-or dialkylamino, and C_1-C_4 alkylacyl. More preferred is for from one to three R3's being halo, the others being hydrogen. Also more preferred is for from one to three R3's being methyl or ethyl, the others being hydrogen. Also preferred is one R3 being dialkylamino, the alkyls having from 1 to about 6 carbon atoms, preferably from about 1 to about 4 carbon atoms, and the others being hydrogen, such R3 preferably being attached to the 4' carbon. More preferred still is for from one to three R3's being independently selected from F, Cl and Br, the others being hydrogen; still more preferred, when two or three R3's are F, Cl or Br, they are the same. Also more preferred is from one to three R3's being unsubstituted methyl, the others being hydrogen. Also more preferred is one or two R3's being trifluoromethyl, the others being hydrogen.

Also preferred are two R3's which are attached to adjacent carbon atoms of the phenyl ring, together being a saturated or unsaturated alkylene or heteroalkylene having from 1 to about 6 carbon atoms and from 0 to about 3 heteroatoms, thus forming a ring

fused to the phenyl, such ring having from about 5 to about 8 ring atoms. Such ring fused to the phenyl preferably has from about 5 to about 6 ring atoms of which from 0 to 2, more preferably 0 or 1, are heteroatoms. Preferred fused rings (including the phenyl to which the R3's are attached) include naphthyl, indolyl, benzimidazoyl, benzofuryl, benzopyranyl. When two R3's form a ring fused with the phenyl, other R3's are preferably H.

In structure 1, R4 is selected from hydrogen, halo, alkyl, aryl, heterocycle, carboxy and its alkyl esters and amides. Preferred R4 is selected from hydrogen, halo, C_1-C_4 alkyl, phenyl. More preferred R4 is selected from hydrogen and unsubstituted and substitituted phenyl; substituents on such phenyl are preferably selected from hydroxy, alkoxy, thio and alkylthio. Most preferred R4 is hydrogen.

In structure 1, R7 is selected from hydrogen, alkyl, aryl, and heterocycle. Non-hydrogen R7 are preferably phenyl, or alkyl having from 1 to about 4 carbon atoms, preferably 1 or 2 carbon atoms. Such non-hydrogen R7 are preferably unsubstituted. Alkyl R7 are preferably saturated. More preferably R7 is hydrogen.

In structure 1, R8 is selected from hydrogen, alkyl, alkylacyl, arylacyl, alkylsulfonyl, and arylsulfonyl. Preferred R8 is selected from hydrogen; C_1-C_6 alkyl, such alkyl being saturated or unsaturated with one double bond and unsubstituted or substituted with phenyl; C_1-C_6 alkylacyl, the alkyl being saturated or unsaturated with one double bond; and phenylacyl. More preferred is the alkyl portions of the aforementioned moieties being C_1-C_4 and saturated. More preferred still is R8 being methyl. Most preferred R8 is hydrogen.

In structure 1, A is aryl or heterocycle. Preferred A includes phenyl, naphthyl, furyl, pyridinyl, pyrrolyl, thienyl, thiazolyl, and imidazolyl; more preferred are phenyl and naphthyl. Also preferred A is phenyl fused with a heterocycle; preferred heterocycles fused with phenyl include furyl, thienyl, dioxanyl, thiazolyl, imidazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, and piperidinyl. When A is phenyl fused with another ring, A is preferably attached to the remainder of structure 1 at a carbon of the phenyl, and the heterocycle ring is preferably fused at any other two adjacent carbon atoms of the phenyl, more preferably at carbons 3-4 of the phenyl.

Each ring carbon of A is unsubstituted or substituted; preferably no more than three

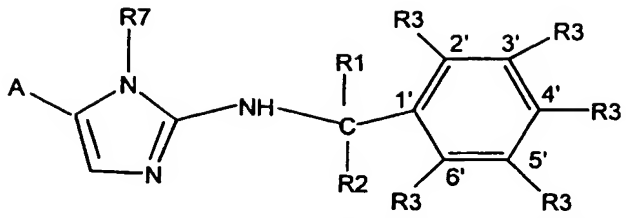
ring carbons of A are substituted; more preferably no more than one ring carbon of A is substituted. Preferred substituents of A, when A is phenyl or naphthyl, are selected from halo, alkyl, aryl, heterocycle, cyano and nitro; also from hydroxy, thio, amino, amide, amido, formyl (acyl), carboxy, carboxamide, and sulfonamide which are unsubstituted or substituted, preferably with alkyl or aryl or heterocycle. More preferred substituents of phenyl and naphthyl A are selected from halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, sulfonamide, alkylsulfonamide, arylsulfonamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides; more preferred still from halo, hydroxy, C_1-C_4 alkoxy, thio, C_1-C_4 alkylthio, C_1-C_4 alkyl esters and amides of carboxy, phenyl, and heterocycle having 5 or 6 ring atoms 1-3 of which are heteroatoms. Preferred substituents of A when A is heterocycle are selected from alkyl, aryl, alkoxy, and aryloxy. More preferred substituents of heterocycle A are selected from C_1-C_4 alkyl or C_1-C_4 alkoxy.

The subject invention includes optical isomers, diastereomers, and enantiomers of the compounds of structure 1. The subject invention includes pharmaceutically-acceptable salts, hydrates, and biohydrolizable esters, amides and imides of such compounds.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic group (e.g., carboxy group), or an anionic salt formed at any basic group (e.g., amino group) on a compound of structure 1. Many pharmaceutically-acceptable salts are known. Preferred cationic salts include the alkali metal salts, such as sodium and potassium, alkaline earth metal salts, such as magnesium and calcium, and organic salts, such as ammonium. Preferred anionic salts include halides, sulfonates, carboxolates, phosphates, and the like. Salts of addition may provide an optical center where once there was none.

The compounds of the subject invention, and salts thereof, may have one or more chiral centers. The invention includes all optical isomers of the compounds of structure 1 and salts thereof, including diastereomers and enanteomers The subject invention includes and contemplates each optical isomer, diastereomer or enanteomer thereof, in purified form, substantially purified form, and mixtures, including racemic mixtures.

Preferred compounds of the subject invention include those having structure 2:



(2)

In structure 2, R1, R2, R3's, R7, and A are as described hereinabove.

In structure 2, R1 is preferably selected from linear alkanyl having from one to four carbon atoms, linear alkenyl having one double bond and from two to four carbon atoms, branched and cyclic alkanyl having from three to five carbon atoms, and branched and cyclic alkenyl having one double bond and from three to five carbon atoms. Such preferred R1 is unsubstituted or substituted with one phenyl, more preferably is unsubstituted. More preferred R1 is selected from methyl, ethyl, ethenyl, n-propyl, i-propyl, n-propenyl, i-propenyl, s-butyl, cyclopropyl, cyclobutyl, and cyclopentyl. More preferred still R1 is selected from methyl, ethyl, ethenyl, i-propyl, and n-propenyl. Still more preferred R1 is methyl.

In structure 2, R2 is preferably hydrogen or includes the same preferences of moieties as stated for R1 in the immediately preceding paragraph, R2 being independent of R1. More preferred R2 is hydrogen or the same as R1. Most preferred R2 is hydrogen.

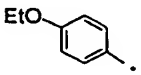
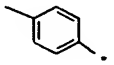
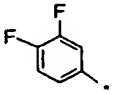
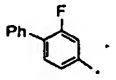
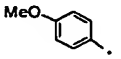
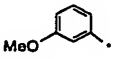
In structure 2, the R3's are preferably selected from all hydrogen; mono-, di-, or trihalo, preferably selected from fluoro, chloro and bromo, preferably in one or more of the 2', 3', 4' and 5' positions; mono- di-, and trimethyl, preferably in one or more of the 2', 3', 4' and 6' positions; and mono- or di-trifluoromethyl, preferably in one or both of the 3' and 5' positions. Also preferred is one R3 being diakylamino, preferably in the 4' position, the two alkyls preferably being the same and preferably having from 1 to 4 carbon atoms, and the other R3's being hydrogen. More preferred combinations of R3's are selected from 4'-fluoro, 4'-chloro, 4'-bromo, 2',4'-difluoro, 2',4'-dichloro, 2',4'-dibromo, 2',4',5'-trifluoro, 2',4',5'-trichloro, 3',4'-difluoro, 3',4'-dichloro, 3',4'-dibromo, 4'-methyl, 2',4'-dimethyl, 2',4',6'-trimethyl, 3'-trifluoromethyl, 3',5'-di-trifluoromethyl, and 4'-dibutylamino; in each cased all other R3's being hydrogen. Also preferred R3 combinations are selected from 2',4'-dihalo and 3',4'-dihalo, where one halo is selected from fluoro, chloro, and

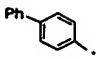
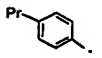
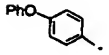
bromo, and the other halo is a different one of those three; more preferably one of such halo is fluoro, all other R3's having hydrogen. Most preferred R3 combinations are selected from 4'-chloro, 4'-bromo, and 2',4'-dichloro, all other R3's being hydrogen.

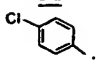
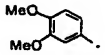
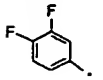
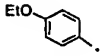
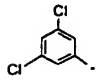
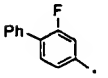
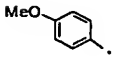
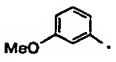
In structure 2, R7 is preferably hydrogen or methyl.

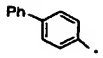
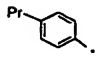
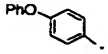
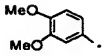
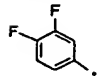
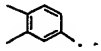
In structure 2, A is preferably unsubstituted or substituted phenyl, naphthyl, or pyridyl; more preferably substituted phenyl, or unsubstituted naphthyl, or unsubstituted 2-pyridyl.

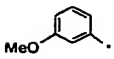
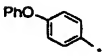
Non-limiting examples of compounds of the subject invention include those of structure 2 wherein R2 is H and R1, R3's, R7, and A are as indicated in the following table (R3's not specified are all hydrogen):

Example	R1	R7	R3's	A
1	Me	H	2',4'-dichloro	
2	Me	H	2',4'-dichloro	
3	Me	H	2',4'-dichloro	
4	Me	H	2',4'-dichloro	
5	Me	H	2',4'-dichloro	
6	Me	H	2',4'-dichloro	
7	Me	H	2',4'-dichloro	
8	Me	H	2',4'-dichloro	
9	Me	H	2',4'-dichloro	
10	Me	H	2',4'-dichloro	
11	Me	H	2',4'-dichloro	

12	Me	H	2',4'-dichloro	
13	Me	H	2',4'-dichloro	
14	Me	H	2',4'-dichloro	
15	Me	H	2',4'-dichloro	
16	Me	H	2',4'-dichloro	

Example	R1	R7	R3's	A
17	Me	H	2',4'-dichloro	
18	Me	H	2',4'-dichloro	
19	Me	H	2',4'-dichloro	
20	Me	H	2',4'-dichloro	
21	Me	H	2',4'-dichloro	
22	Me	H	2',4'-dichloro	
23	Me	H	2',4'-dichloro	
24	Me	H	4'-chloro	
25	Me	H	4'-chloro	
26	Me	H	4'-chloro	
27	Me	H	4'-chloro	
28	Me	H	4'-chloro	
29	Me	H	4'-chloro	
30	Me	H	4'-chloro	
31	Me	H	4'-chloro	
32	Me	H	4'-chloro	
33	Me	H	4'-chloro	

Example	R1	R7	R3's	A
34	Me	H	4'-chloro	
35	Me	H	4'-chloro	
36	Me	H	4'-chloro	
37	Me	H	4'-chloro	
38	Me	H	4'-chloro	
39	Me	H	4'-chloro	
40	Me	H	4'-chloro	
41	Me	H	4'-chloro	
42	Me	H	4'-chloro	
43	Me	H	4'-chloro	
44	Me	H	4'-chloro	
45	Me	H	4'-chloro	
46	Me	H	4'-chloro	
47	Et	H	4'-fluoro	
48	Me	H	H	
49	Et	H	H	
50	Me	H	H	
51	Et	H	H	
52	Me	H	4'-fluoro	

Example	R1	R7	R3's	A
53	Me	H	2',4'-dichloro	
54	Me	H	4'-chloro	
55	Me	H	H	
56	Me	H	4'-fluoro	
57	Et	H	4'-fluoro	
58	Me	Me	2',4'-dichloro	
59	Me	Me	2',4'-dichloro	
60	Me	Me	2',4'-dichloro	
61	Me	Me	2',4'-dichloro	
62	Me	Me	2',4'-dichloro	
63	Me	Me	2',4'-dichloro	
64	Me	Me	4'-chloro	
65	Me	Me	4'-chloro	
66	Me	Me	4'-chloro	
67	Et	Me	4'-fluoro	
68	Et	Me	H	
69	Me	Me	4'-fluoro	
70	Me	Me	H	

In addition, it is recognized that for purification, administration, and the like, the salts and other derivatives of the above compounds can be used. Thus a pharmaceutically-acceptable salt, hydrate, or biohydrolizable ester, amide or imide thereof is contemplated as part of the subject invention.

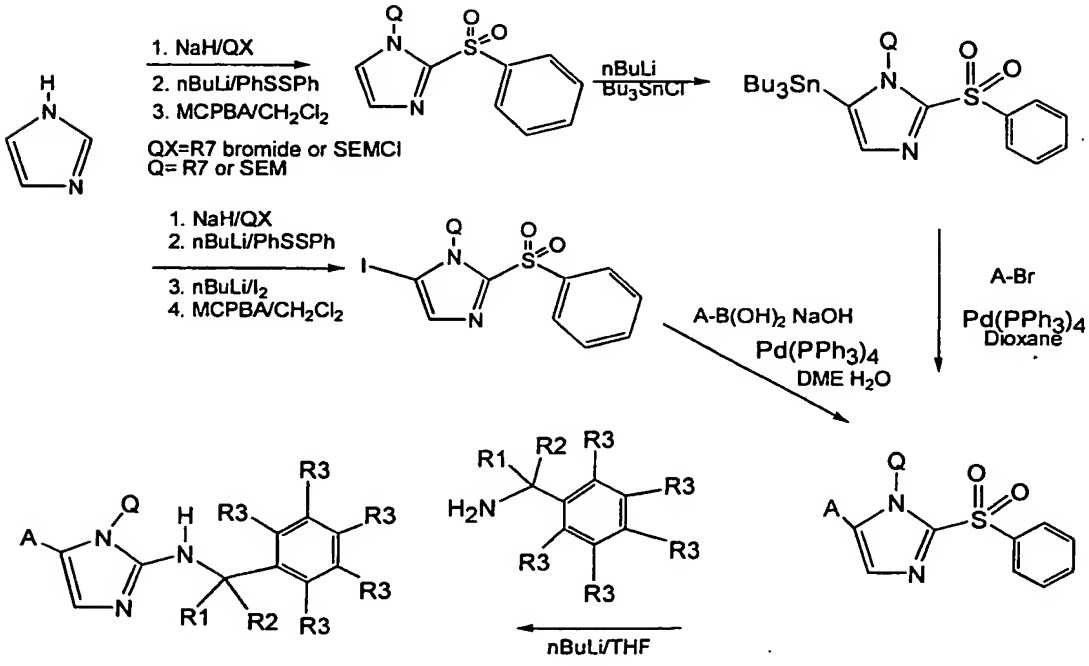
Methods of Making the Compounds

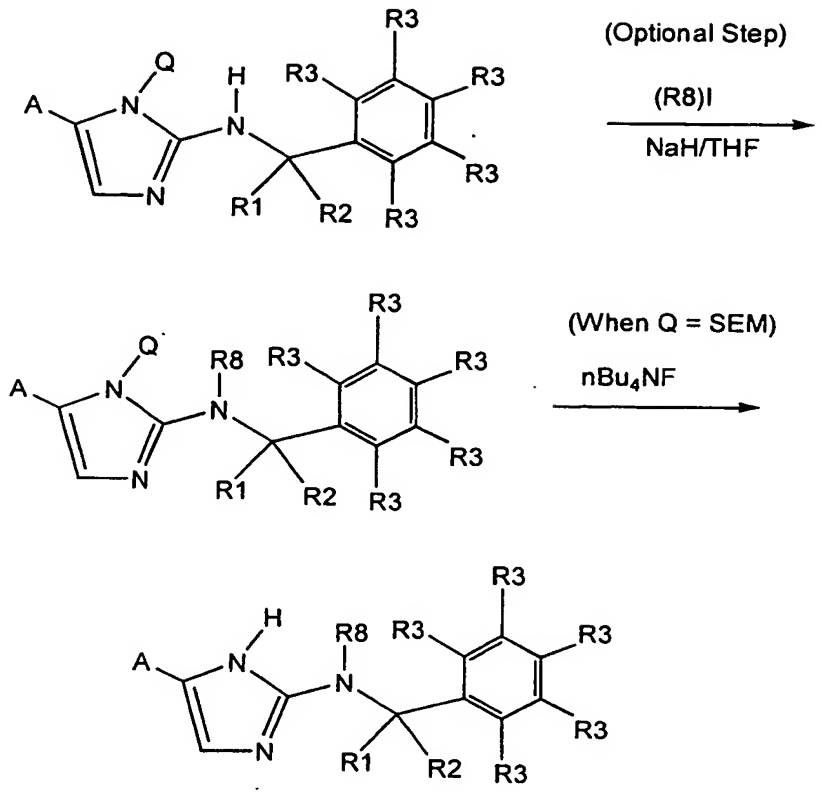
In making the compounds of the subject invention, the order of synthetic steps may be varied to increase yield of desired product. The skilled artisan will recognize that the judicious choice of reactants, solvents, and temperatures is important in successful synthesis. The starting materials used in preparing the subject compounds are known, made by known methods, or are commercially available.

It is recognized that the skilled artisan can readily carry out standard manipulations of organic compounds without further direction. These include, but are not limited to, reduction, oxidation, acylation, substitution, etherification, esterification, sulfonation, and the like. Examples of these manipulations are discussed in standard texts.

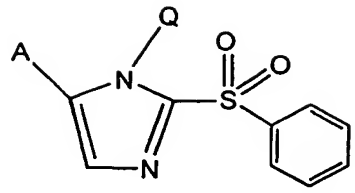
The following general schemes can be used for synthesizing compounds of the subject invention. In these schemes, R1, R2, R3, R4, R7, R8, and A are as defined hereinabove. Non-conventional symbols and abbreviations for other moieties and chemicals, which may not be clear to the skilled chemist, are defined in the Examples hereinbelow.

General Scheme I



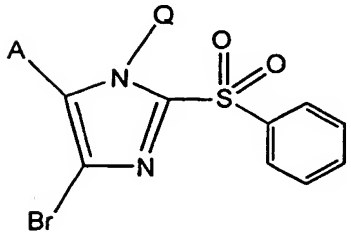

(Optional Step)
(R8)I
NaH/THF
(When Q = SEM)
nBu4NF
A
Q
H
R8
R1
R2
R3
N

General Scheme II



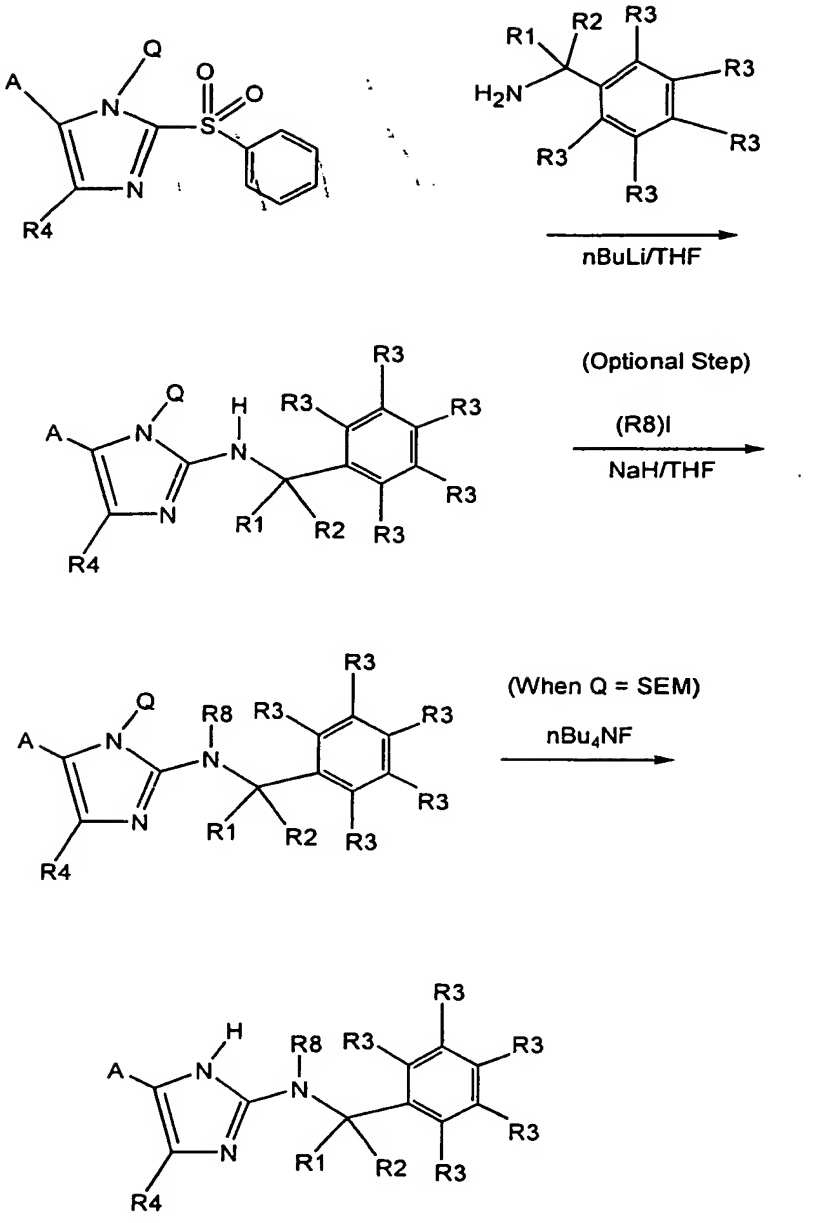
Q = R7 or SEM

NBS



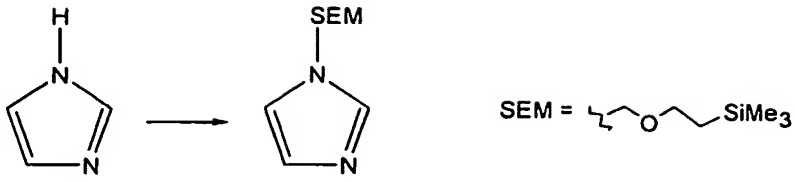
$Pd(PPh_3)_4$
Toluene

$R4\text{-}SnMe_3$
or $R4\text{-}B(OH)_2$



The following examples provide further information regarding synthesis of the subject invention compounds. The same procedures can be followed for preparation of N-methyl imidazole compounds with the methyl group in the place of the SEM group.

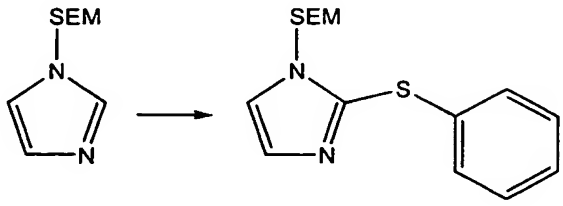
Precursor Example 1



A

A suspended solution of NaH (6.5 g, 0.162 mol, washed with hexane twice) in anhydrous DMF (300 ml) is cooled in an ice/acetone bath (bath temp. -15 °C). Solid imidazole (10 g, 0.145 mol) is added in small portions and the mixture is stirred at room temperature (r.t.) for 0.5 h; the solution becomes clear. SEM-Cl (25 g, 0.150 mol) is added dropwise by a syringe pump at r.t. over 1 h; NaCl precipitates during the addition. The mixture is stirred at r.t. for about 1 h. Progress of the reaction is monitored by TLC (CH_2Cl_2/MeOH, 9:1). H_2O (10 ml) is added with caution to quench the reaction. The solvent is evaporated in vacuo. The residue is dissolved in Et_2O (200 ml) and washed with H_2O (4 x 50ml), brine (50 ml), dried ($MgSO_4$), filtered, and evaporated in vacuo to give compound A as an orange liquid.

Precursor Example 2

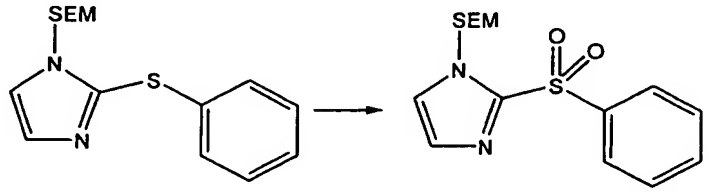


A B

To a solution of SEM-protected imidazole A (1.48 g, 7.50 mmol) in dry THF (75 ml) under argon at -78 °C, n-BuLi (1.6 M in hexane) (6 ml, 9.60 mmol) is added dropwise and the mixture is stirred at -78 °C for 30 min. Phenyl disulfide (2.1 g, 9.60 mmol) in THF (2 ml) is then added dropwise. The dry ice/acetone bath is replaced with an ice bath after this addition. The mixture is stirred at 0 °C for 1 h, then at r.t. for 1 h. Progress is monitored by TLC (CH_2Cl_2/MeOH, 9:1). H_2O (5 ml) is added to quench the reaction.

The solvent is evaporated in vacuo, and the residue is dissolved in Et_2O, washed with 5% $NaHCO_3$ (3 x 20ml), brine (20 ml), dried ($MgSO_4$), evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc 3:1) to give **B** as a yellow oil.

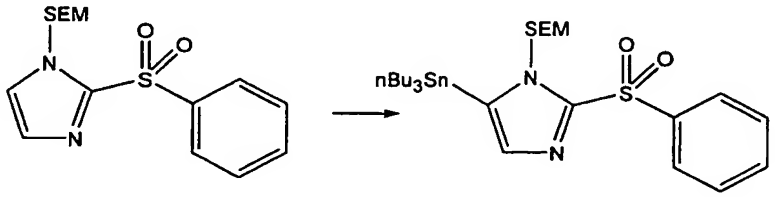
Precursor Example 3



B C

3-chloroperoxybenzoic acid (MCPBA, 80-85%) (17.03 g, 78.9 mol) is added to a solution of SEM-protected 2-phenylsulfide imidazole **B** (9.71 g, 31.6 mmol) in anhydrous CH_2Cl_2 (160mL), and the reaction is stirred under argon at room temperature for 15 hours. Progress monitored by TLC (hexane/EtOAc, 3:1). Sodium thiosulfate (3.9 g) is added to remove excess MCPBA. The mixture is filtered. The filtrate is washed with 5% Na_2CO_3 (3 x 150 mL), brine (150 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc 3:1) to give **C** as a light yellow oil.

Precursor Example 4

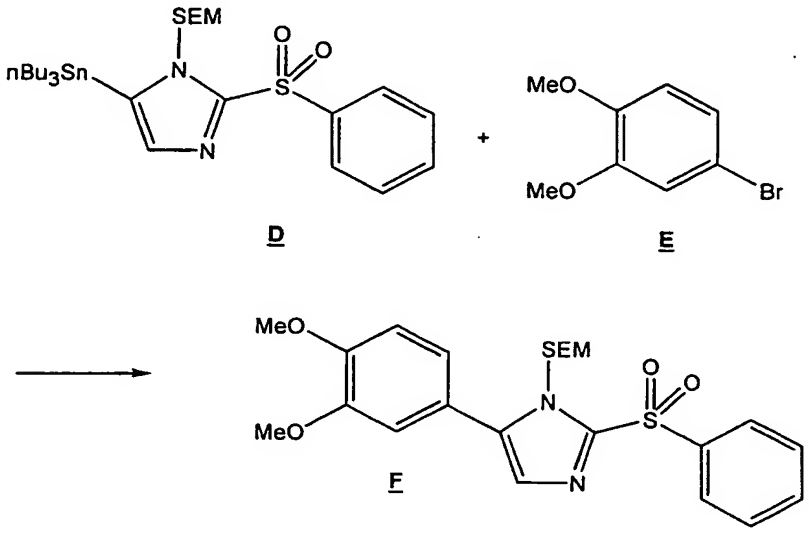


C D

To a solution of SEM-protected 2-phenylsulfone imidazole **C** (8.61 g, 25.4 mmol) in anhydrous THF (250 mL) under argon at -78 °C, n-BuLi (1.6 M in hexane) (19.0 mL, 30.0 mmol) is added dropwise by a syringe pump; the solution is stirred at -78 °C for 30 minutes. Tributyltin chloride (6.9 mL, 25.4 mmol) is added dropwise by a syringe

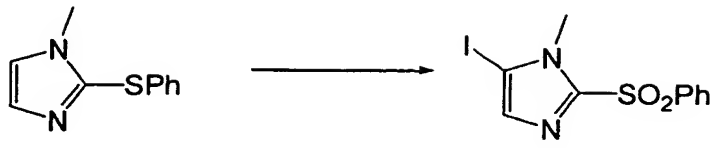
pump. The mixture is stirred at room temperature for one hour. Progress is monitored by TLC (hexane/EtOAc, 9:1). H_2O (30 mL) is added to quench the reaction. The solvent is evaporated in vacuo. The residue is dissolved in ether (550 mL) and washed with saturated NH_4Cl (3 x 150 mL), brine (150 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, gradient: hexane (500 mL), hexane/EtOAc, 50:1; hexane/EtOAc, 12:1) to give D as a clear oil.

Precursor Example 5



$Pd(PPh_3)_4$ (0.0177g, 0.015 mmol) is added to a solution of stannylimidazole D (0.51 g, 0.80 mmol), 4,5-dimethoxy-2-(2-hydroxyethyl)phenyl bromide E (0.33 g, 1.1 mmol), and LiCl (0.087 g, 2.1 mmol) in anhydrous dioxane (4.0 mL) at room temperature. A few crystals (~ 2 mg) of a radical scavenger, 2,6-di-tert-butyl-4-methylphenol, is added and the reaction is heated to reflux under argon for 5 hours. The reaction is cooled to room temperature and treated with a 1:1 mixture of ether and saturated aqueous KF solution (10 mL) for 15 hours. Progress is monitored by TLC (hexane/EtOAc, 3:1). The mixture is filtered through a pad of Celite with ether rinses. The filtrate is washed with water (3 x 12 mL), brine (3 x 12 mL), dried ($MgSO_4$), filtered, evaporated in vacuo, and purified by chromatography (silica gel, hexane/EtOAc, 2:3) to give F as an orange oil.

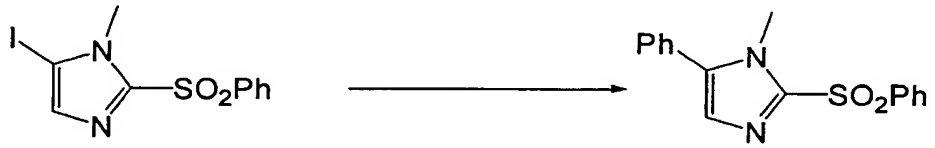
Precusor Eample 6



A B

5.13 g (26.3 mmol) of **A** is dissolved in 40 ml THF, cooled to -78 °C, and 11.9 ml of n-BuLi in hexane (2.5 M, 28.9 mmol) is added slowly. After 1 h, a solution of 7.54 g (28.9 mmol) of iodine in 15 ml THF is added, and the reaction is stirred at -78 °C for 1.5 h. The reaction is then quenched with 150 ml $NaHCO_3$ (aq.) and $Na_2S_2O_3$ (aq.) to remove the excess iodine. The resulting solution is then extracted with EtOAc (2 x 100 ml) and methylene chloride (2 x 100 ml), and the combined organic layers are dried over $MgSO_4$, filtered and stripped to a pale yellow solid which is used without further purification (8.3 g). The solid is dissolved in 150 ml methylene chloride and 11.64 g (52.6 mmol) of MCPBA (80% by weight) is added. The reaction is stirred at room temperature for 14 h, and then diluted with 450 ml methylene chloride. The resulting solution is washed with Na_2CO_3 (aq., 2 x 450 ml), and the water is back extracted with methylene chloride (450 ml). The combined organic layers are then dried over $MgSO_4$, filtered and stripped to yield 7.76 g (83%) of the desired product (**B**) as a pale yellow solid.

Precusor Eample 7

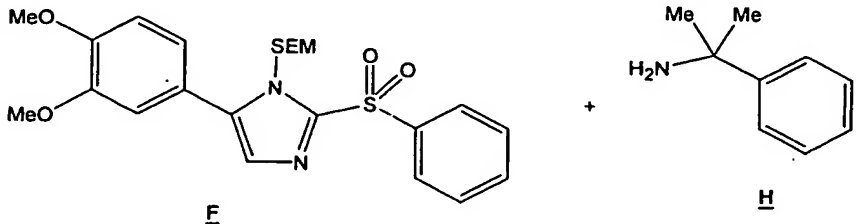


A B

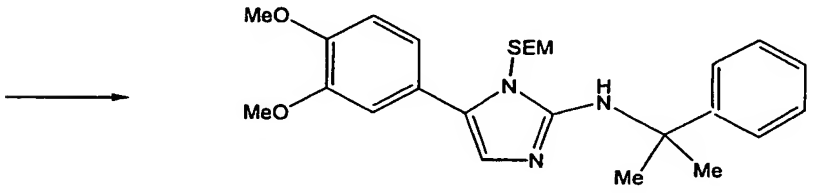
2.0 g (5.75 mmol) of **A** and 840 mg (6.88 mmol) phenyl boronic acid are dissolved in 13.8 ml 1.0 N NaOH and 45 ml DME. The solution is degassed by bubbling a stream of N_2 through the solution, 220 mg (0.2 mmol) $Pd(PPh_3)_4$ is added, and the reaction is heated to reflux. After 19 h the reaction is cooled to room temperature and poured into

150 ml $NaHCO_3$ (aq.). The resulting solution is then extracted with methylene chloride (3 x 150 ml), and the combined organic layers are dried over $MgSO_4$, filtered and stripped to a solid. Chromatography with 1/1 hexane/EtOAc provided 1.23 g (73%) of the desired product (**B**) as a pale yellow solid.

Precursor Example 8



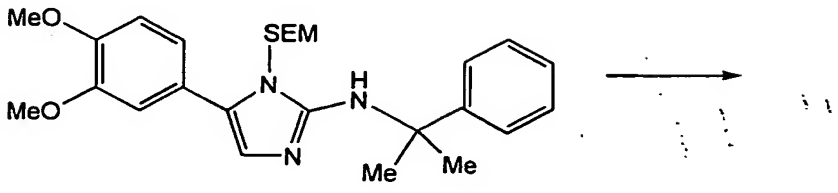
F H



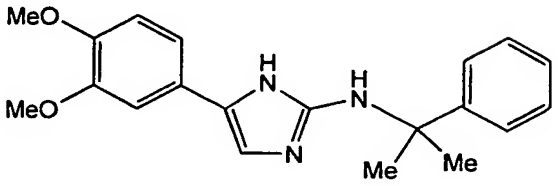
J

In a 25 mL single neck round bottom flask, equipped with a magnetic stir bar, argon inlet, and rubber septum, 1-methyl-1-phenyl-ethylamine (H) (164 mg, 1.2 mmol) in anhydrous THF under argon atmosphere is cooled to 0 °C. nBuLi in hexane (0.5 mL, 2.4 M) is added to the solution slowly. The reaction turns light yellow. After stirring for 45 minutes, compound F (150 mg, 0.405 mmol) in THF (1 mL) is added. The solution is warmed to room temperature, and is further heated to reflux for 12 h. TLC (CH_2Cl_2:CH_3OH, 99:1) indicates completion of the reaction. The solution is quenched with MeOH and evaporated to give a residue which is redissoleved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine, and dried over Na_2SO_4. The crude product, after filtration and evaporation in high vacuum in order to remove any excess amine H, is purified by chromatography (CH_2Cl_2:CH_3OH, 99:1) to provide compound J.

Invention Compound Example I



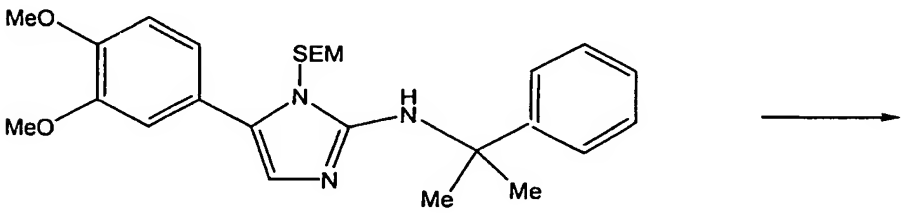
J



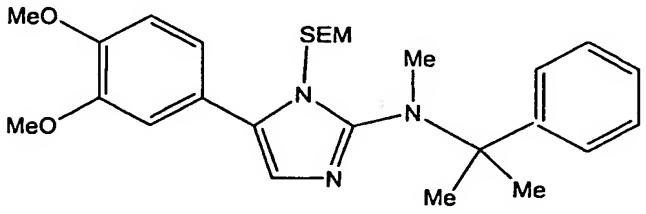
X

To a solution of J (50 mg, 0.1 mmole) in THF (1 mL), nBu_4NF (52 mg, 0.2 mmole) dissolved in THF (0.5 mL) is added dropwise, The reaction mixture is stirred at ambient temperature for 4 hours. The solvent is evaporated to give a residue. This residue is dissolved in CH_2Cl_2 and washed with 5% Na_2CO_3 aqueous and water, and dried over Na_2SO_4. Removal of the solvent gives a crude product. Column chromatography using eluant CH_2Cl_2:MeOH system affords subject invention compound **X**.

Precursor Example 9



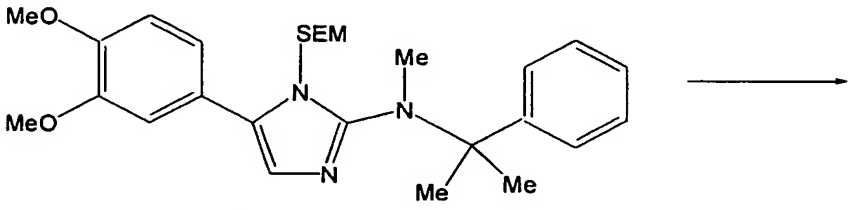
J



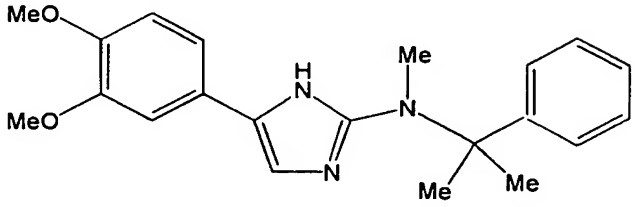
P

In a 25 mL single neck round bottom flask, compound J (181 mg, 0.5 mmol) in anhydrous THF (10 mL) under argon atmosphere is cooled to 0 °C, then NaH (18 mg) pre-washed with hexane is added as a suspension in hexane to the solution. After stirring for 15 minutes, methyl iodide (71 mg, 0.5 mmoll) in THF (0.5 mL) is added. The solution is warmed to room temperature, and further heated to reflux for 2 h to complete the reaction. The solution is quenched with MeOH and evaporated to give a residue which is redissolved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine and dried over Na_2SO_4. The crude product is purified by chromatography (CH_2Cl_2:CH_3OH from 99:1 to 95:5) to provide compound P.

Invention Compound Example II



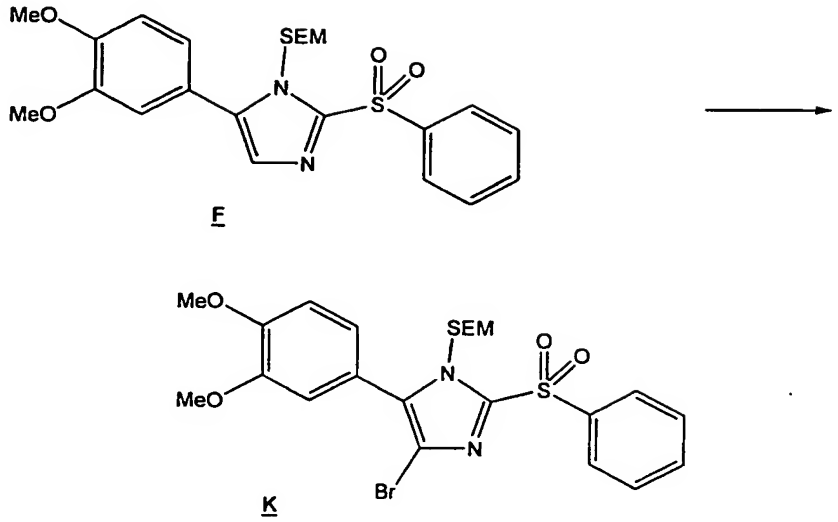
P



Y

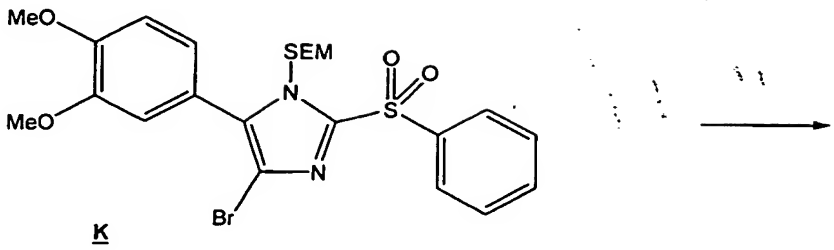
Conversion of P to subject invention compound Y is is acheived using the same procedure as described above to convert compound J to compound X..

Precursor Example 10

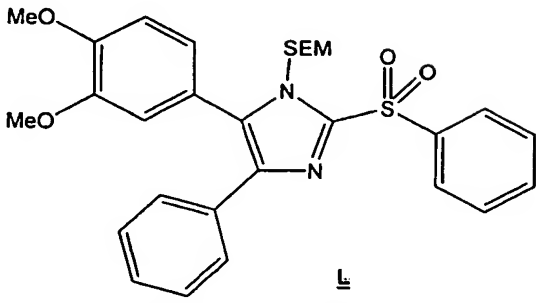


N-bromosuccinimide (NBS) solid (98 mg, 0.26 mmol) is added to a solution of compound F (0.5 mmol) in 15 mL of CCl_4. Radical initiator benzoyl peroxide (2 mol %) is subsequently added. The flask is placed into a 90 °C oil bath. After 10 min stirring, the reaction is complete. Filtration of the mixture through a celite pad, and evaporation of the filtrate gives a residue. Purification by chromatography (EtOAc:hexane, 1:3 to 1:1) affords compound K.

Precursor Example 11



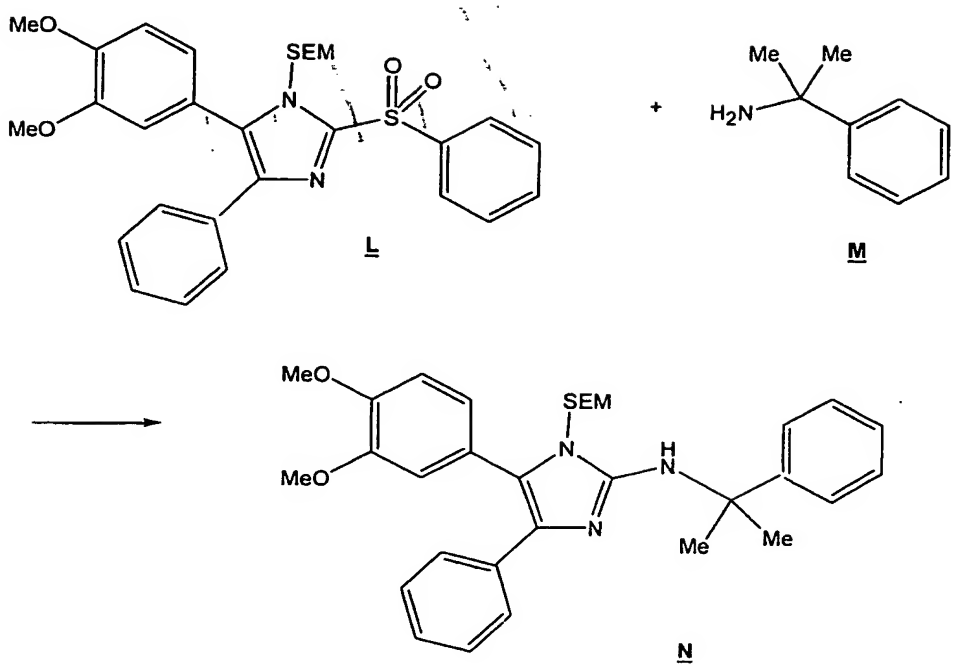
K



L

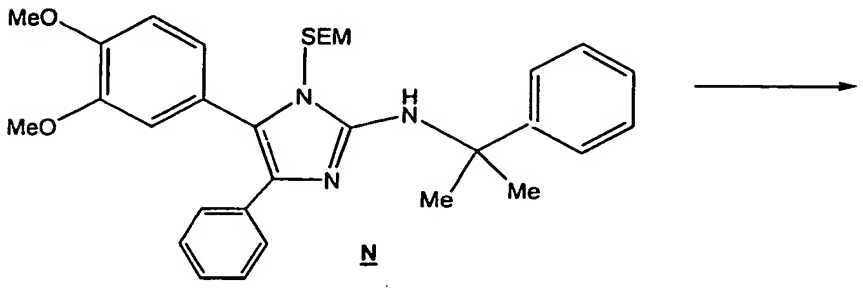
To a solution of **K** (0.22mmol) and $Pd(PPh_3)_4$ (13mg, 0.056mmol) in 7 mL of anhydrous toluene are added phenyltributyltin (0.26mmol) and a few crystals (~ 2 mg) of 2,6-di-tert-butyl-4-methylphenol. The reaction mixture is allowed to reflux at 110 °C under nitrogen for 6 hours to complete the reaction. The reaction mixture is allowed to cool, and is then diluted with 1-2 mL of ethyl acetate (EtOAc). The resultant mixture is washed with water, then brine, extracted with CH_2Cl_2, dried over Na_2SO_4, and filtered. The filtrate is treated with 3 mL of 30% aqueous KF at room temperature for 2h. The solid is filtered off. The filtrate is diluted with CH_2Cl_2 and washed with water, 30% aqueous NH_4OH (3X), brine, extracted with EtOAc, dried (Na_2SO_4), and concentrated *in vacuo* to yield crude product. Chromatography purification (silica gel, EtOAc:hexane, 1:1 to 1:0) yields compound **L**.

Precursor Example 12

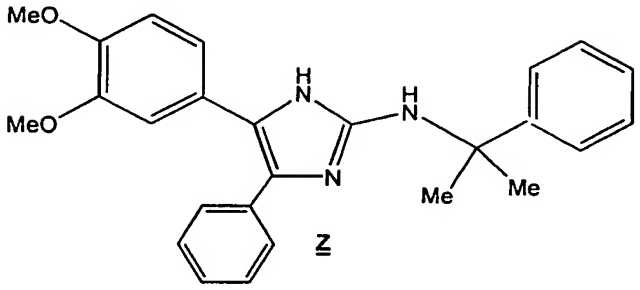


In a 25 mL single neck round bottom flask, equipped with a magnetic stir bar, argon inlet, and rubber septum, (1-methyl-1-phenyl-ethylamine) (M) (1.2 mmol) in anhydrous THF under argon atmosphere is cooled to 0 °C. nBuLi in hexane (0.5 mL, 2.4 M) is added slowly to the solution. The reaction turns light yellow. After stirring for 45 minutes, compound L (180 mg, 0.405 mmol) in THF (1 mL) is added. The solution is warmed to room temperature, and is further heated to reflux for 12 h to complete the reaction. The solution is quenched with MeOH and evaporated to give a residue which is redissoleved in CH_2Cl_2, washed with aqueous $NaHCO_3$ (5%), H_2O, brine and dried over Na_2SO_4. The crude product, after filtration and evaporation in high vacuum in order to remove excess amine M, is purified by chromatography to provide compound N.

Subject Invention Example III



N



Z

Conversion of N to subject invention compound Z is acheived using the same procedure as described above to convert compound J to compound X.

Compositions of the Invention

A composition of the subject invention comprises:

a) a safe and effective amount of a compound of the invention; and

b) a pharmaceutically-acceptable excipient.

Typically, such composition comprises several excipients. It may also optionally comprise other active compounds which do not substantially interfere with the activity of the subject invention compound.

The compositions of the subject invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical or parenteral administration. Compositions of the subject invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a subject compound that is suitable for administration to a human or lower animal subject, in a single dose, according

to good medical practice.

As used herein, a "safe and effective amount" of a subject compound is an amount large enough to significantly induce a positive modification in the symptoms and/or condition to be treated in a host, but small enough to avoid serious adverse side effects in the host (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio. The safe and effective amount will vary with such factors as the particular condition being treated, the age and physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, and the dosage regimen employed.

The term "pharmaceutically-acceptable excipient", as used herein, includes physiologically inert, pharmacologically inactive substances which are compatible with the physical and chemical characteristics of the subject invention compound used, and which are of sufficiently high purity and sufficiently low toxicity to be suitable for administration to a human or lower animal. The term "compatible", as used herein, means that the excipients of the subject composition are capable of being commingled with the subject invention compound, and with each other in a manner such that there is no interaction which would substantially reduce the pharmaceutical efficacy of the compound, under ordinary use situations.

Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable excipients well-known in the art may be used. Excipients include, but are not limited to, polymers, resins, plasticizers, fillers, binders, lubricants, glidants, disintegrants, solvents, co-solvents, buffer systems, surfactants, preservatives, sweetening agents, flavoring agents, and dyes or pigments. The amount of excipients employed in conjunction with the subject compound is sufficient to provide a practical quantity of material for administration per unit dose of the subject compound.

Some examples of substances which can serve as pharmaceutically-acceptable excipients are sugars, such as lactose, dextrose, glucose and sucrose; starches, such as cornstarch and potato starch; cellulose and its derivatives, such as methylcellulose, sodium carboxymethylcellulose, ethylcellulose, hydroxypropylcellulose and cellulose acetate; polymers, such as povidone and carbomers; powdered tragacanth; gums, such as xanthan,

guar and acacia; malt; solid lubricants, such as stearic acid, magnesium stearate, and talc; inorganic fillers, such as calcium phosphates and calcium sulfate; disintigrants, such as sodium starch glycolate, crospovidone, croscarmelose sodium, and microcrystalline cellulose; encapsulating and coating materials, such as gelatins, waxes, and cellulose derivatives; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of the obroma; polyols such as propylene glycol, glycerin, sorbitol, mannitol, and polyethylene glycol; alginic acid; surfactants such as the Tweens®, alkyl sulfate salts, salts of fatty acids, sucrose esters; ethyl oleate; coloring agents; flavoring agents; tableting agents; stabilizers; antioxidants; preservatives; solvents, such as ethanol, pyrogen-free water; isotonic saline; and buffer solutions, such as phosphoric, tartaric, citric, and acetic acids, and their sodium, potassium, and ammonium salts.

Preferred compositions of the subject invention are oral dosage forms. The term "oral dosage form", as used herein, means any pharmaceutical composition intended to be systemically administered to an individual by delivering the composition via the mouth to the gastrointestinal tract of an individual. Preferred are oral unit dosage forms, such as tablets, coated or non-coated, and capsules, hard or soft gel. Subject oral unit dosage form compositions comprise preferably at least about 4 mg, more preferably at least about 20 mg, more preferably still at least about 100 mg, and preferably at most about 1000 mg, more preferably at most about 500 mg, more preferably still at most about 250 mg, of a subject compound. Subject oral dosage form compositions comprise preferably at least about 1%, more preferably at least about 10%, and preferably at most about 70%, more preferably at most about 40%, of a subject compound; and comprise preferably at least about 30%, more preferably at least about 60%, and preferably at most about 99%, more preferably at most about 90%, pharmaceutically-acceptable excipients.

Parenteral dosage forms are also preferred subject invention compositions. The term "parenteral dosage form", as used herein, means any pharmaceutical composition intended to be systemically administered to a human or lower animal via delivery of a solution or emulsion containing the active ingredient, by puncturing the skin of the individual, in order to deliver the solution or emulsion to the circulatory system of the individual either by intravenous, intramuscular, intraperitoneal or subcutaneous injection.

Subject parenteral unit dosage form compositions comprise preferably at least about 1 mg, more preferably at least about 6 mg, more preferably still at least about 30 mg, and preferably at most about 400 mg, more preferably at most about 100 mg, more preferably still at most about 40 mg, of a subject compound. Subject parenteral dosage form compositions comprise preferably at least about 1%, more preferably at least about 5%, and preferably at most about 20%, more preferably at most about 10%, of a subject compound; and comprises preferably at least about 80%, more preferably at least about 90%, and preferably at most about 99%, more preferably at most about 95%, pharmaceutically-acceptable excipients. In addition, dosages for injection may be prepared in dried or lyophilized form. Such forms can be reconstituted with water, saline solution, or a buffer solution, depending on the preparation of the dosage form. Such forms may be packaged as individual dosages or multiple dosages for easier handling. Where lyophilized or dried dosages are used, the reconstituted dosage form is preferably isotonic, and at a physiologically compatible pH, and comprises the subject compound and excipients in the amounts and percentages indicated previously in this paragraph.

Methods of Treatment Using the Compounds

Subject invention compounds have demonstrated pharmacological activity in processes known to be associated with one or more of cardiovascular activity, inflammatory mechanisms, oncology, and regulation of protein transport from cells. The subject invention includes methods of using the above compounds of the subject invention for therapeutic or preventative treatment of one or more of the following diseases or disorders: congestive heart failure, arrhythmia, hypotension, cardiac reperfusion injury, arteriosclerosis, restenosis, vascular tone, bacterial infection, cancer, Kaposi's sarcoma, psoriasis, migraine, nasal congestion, allergic responses, rheumatoid arthritis, and osteoporosis. Such methods comprise administering to a human or lower animal in need of such treatment or prevention a safe and effective amount of a subject invention compound.

For preferred oral administration of compounds and/or compositions of the subject invention, preferably at least about 0.1 mg/kg, more preferably at least about 0.5 mg/kg, more preferably still at least about 2 mg/kg, and preferably at most about 20 mg/kg, more

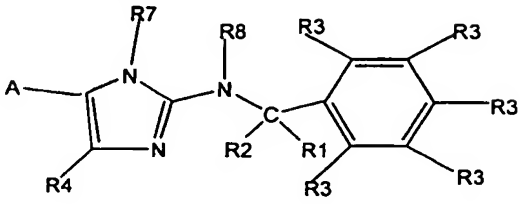
preferably at most about 5 mg/kg, more preferably still at most about 2 mg/kg, of a subject compound is administered to a human or lower animal, preferably at least about 1 time, more preferably at least about 2 times, and preferably at most about 4 times, more preferably at most about 2 times, daily. Treatment duration using such oral daily dosages is dependent on the disease or disorder being treated; it is preferably at least about 1 day, more preferably at least about 3 days, more preferably still at least 7 days, and preferably at most about 5 years, more preferably at most about 60 days, more preferably still at most about 15 days.

For preferred parenteral administration of compounds and/or compositions of the subject invention, preferably at least about 0.04 mg/kg, more preferably at least about 0.2 mg/kg, more preferably still at least about 1 mg/kg, and preferably at most about 10 mg/kg, more preferably at most about 4 mg/kg, more preferably still at most about 1 mg/kg, of a subject compound is administered to a human or lower animal, preferably at least about 1 time, more preferably at least about 2 times, and preferably at most about 4 times, more preferably at most about 2 times, daily. Treatment duration using such parenteral daily dosages is dependent on the disease or disorder being treated; it is preferably at least about 1 day, more preferably at least about 3 days, more preferably still at least 7 days, and preferably at most about 60 days, more preferably at most about 20 days, more preferably still at most about 5 days.

While particular embodiments of the subject invention have been described, it will be obvious to those skilled in the arts that various changes and modifications of the subject invention can be made without departing from the spirit and scope of the invention. It is intended to cover, in the appended claims, all such modifications that are within the scope of this invention.

WHAT IS CLAIMED:

1. A compound having the structure:



wherein:

(a) R1 is selected from the group consisting of alkyl, aryl, and heterocycle;

(b) R2 is selected from the group consisting of hydrogen, alkyl, aryl, and heterocycle;

(c) each R3 is independently selected from the group consisting of hydrogen, halo, alkyl, aryl, heterocycle, nitro, cyano, and unsubstituted or alkyl- or aryl- or heterocycle-substituted hydroxy, thio, amino, amide, formyl (acyl), carboxy, and carboxamide; two R3's may optionally together be alkylene or heteroalkylene, thereby forming a fused ring with the phenyl to which they are attached;

(d) R4 is selected from the group consisting of hydrogen, halo, alkyl, aryl, heterocycle, and carboxy and its alkyl and aryl esters and amides;

(e) R7 is selected from the group consisting of hydrogen, alkyl, aryl, and heterocycle;

(f) R8 is selected from the group consisting of hydrogen, alkyl, alkylacyl, arylacyl, alkylsulfonyl, and arylsulfonyl;

(g) A is aryl or heterocycle;

and an optical isomer, diastereomer or enantiomer thereof; a pharmaceutically acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof.

2. The compound of Claim 1 wherein:

(a) R1 is linear, branched or cyclic C_1-C_6 alkanyl or alkenyl, unsubstituted or substituted with one phenyl;

(b) R2 is hydrogen or linear, branched or cyclic C_1-C_6 alkanyl or alkenyl, unsubstituted or substituted with one phenyl;

(c) each R3 is independently selected from the group consisting of hydrogen, halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides; or two R3's together are alkylene or heteroalkylene and, with the carbons to which they are attached, form a fused cycloalkyl, aryl or heterocycle ring having from 5-8 ring atoms;

(d) R4 is selected from the group consisting of hydrogen, halo, alkyl, C_1-C_4 alkyl, and phenyl;

(e) R7 is selected from the group consisting of hydrogen, C_1-C_4 alkyl and phenyl;

(f) R8 is selected from the group consisting of hydrogen, C_1-C_6 alkyl, and phenyl;

(g) A is selected from the group consisting of phenyl, naphthyl, furyl, pyridinyl, pyrrolyl, thienyl, thiazolyl, imidazolyl, and phenyl fused with heterocycle selected from the group consisting of furyl, thienyl, dioxanyl, thiazolyl, imidazolyl, pyridinyl, pyrrolyl, pyrrolidinyl, and piperidinyl.

3. The compound of Claim 2 wherein:

(a) R1 is unsubstituted C_1-C_5 linear, or C_3-C_5 branched or cyclic, alkanyl; or unsubstituted C_2-C_5 linear, or C_3-C_5 branched or cyclic, alkenyl having one double bond;

(b) R2 is selected from the group consisting of hydrogen; unsubstituted C_1-C_5 linear, or C_3-C_5 branched or cyclic, alkanyl; or unsubstituted C_2-C_5 linear, or C_3-C_5 branched or cyclic, alkenyl having one double bond;

(c) each R3 is independently selected from the group consisting of hydrogen, halo, C_1-C_4 alkyl, thio, C_1-C_4 alkylthio, C_1-C_4 mono- or dialkylamino, C_1-C_4 alkylacyl.

4. The compound of Claim 3 wherein A is phenyl or naphthyl, unsubstituted or

substituted with from one to about three substituents selected from the group consisting of halo, alkyl, aryl, heterocycle, hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, amide, alkylamide, arylamide, sulfonamide, alkylsulfonamide, arylsulfonamide, formyl, alkylacyl, arylacyl, carboxy and its alkyl and aryl esters and amides; and preferably R7 is hydrogen or methyl, and R8 is hydrogen or methyl.

5. The compound of Claim 4 wherein R1 is selected from the group consisting of methyl, ethyl, ethenyl, n-propyl, i-propyl, n-propenyl, i-propenyl, s-butyl, cyclopropyl, cyclobutyl, and cyclopentyl, preferably R1, is methyl or ethyl.

6. The compound of any of Claims 2 and 5 wherein R2 is hydrogen or methyl and R4 and R8 are hydrogen, preferably R2 is hydrogen and preferably R7 is hydrogen.

7. The compound of Claim 6 wherein A is phenyl, unsubstituted or substituted with from one to about three substituents selected from the group consisting of halo, hydroxy, C_1-C_4 alkoxy, thio, C_1-C_4 alkylthio, C_1-C_4 alkyl esters and amides of carboxy, phenyl, and heterocycle having 5 or 6 ring atoms 1-3 of which are heteroatoms.

8. A composition comprising:

(a) a safe and effective amount of a compound of any of Claims 1, 4 and 6; and

(b) a pharmaceutically-acceptable excipient.

9. A method for treating or preventing congestive heart failure, hypotension, cardiac arrhythmia, cardiac reperfusion injury, nasal congestion or migraine comprising administering to a human or lower animal in need thereof a safe and effective amount of a compound of any of Claims 1, 4 and 6.

10. A method for treating or preventing a disease or disorder caused by cellular protein transport including, but not limited to, osteoporosis, rheumatoid arthritis, allergic responses, restenosis, vascular tone, cancer, Kaposi's sarcoma, psoriasis, and bacterial infections, comprising administering to a human or lower animal in need thereof a safe and effective amount of a compound of any of Claims 1, 4 and 6.

INTERNATIONAL SEARCH REPORT

Interr ›nal Application No
PCT/US 00/33820

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D233/88 C07D401/04 A61K31/415 //(C07D401/04,233:00, 213:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, PAJ, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	FR 1 508 888 A (J.R. GEIGY S.A.) 20 March 1968 (1968-03-20) page 1; résumé ---	1-10
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A	EP 0 044 486 A (DU PONT) 27 January 1982 (1982-01-27) abstract; claims ---	1-10
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 March 2001	19/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

INTERNATIONAL SEARCH REPORT

Interr ›nal Application No
PCT/US 00/33820

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Inter ...nal Application No
PCT/US 00/33820

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